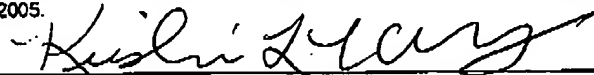


Attorney Docket No. PC7180

I hereby certify that this correspondence is being facsimile transmitted to the United States Patent and Trademark Office, Fax No. (571) 273-7744, on July 26, 2005.

By



(Signature of person signing Certificate)  
Kristina L. Konstas

(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE: U.S. Patent No. 4,831,031

ISSUED: May 16, 1989

: FROM: Serial No. 06/146,886

TO: John A. Lowe, III, et al.

: FILED: January 22, 1988

TITLE: ARYL PIPERAZINYL- (C2 or C4)  
ALKYLENE HETEROCYCLIC  
COMPOUNDS HAVING  
NEUROLEPTIC ACTIVITY

Commissioner for Patents  
PO Box 1450  
Alexandria, VA 22313-1450

Sir,

SUPPLEMENT TO MARCH 30, 2001 PATENT TERM EXTENSION APPLICATION

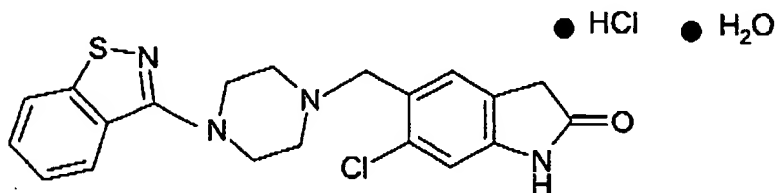
This Supplement is being filed in connection with the Patent Term Extension Application filed on March 30, 2001 with the United States Patent Office in connection with the above-identified Patent (hereinafter "Patent '031"). Applicant is filing this Supplement to point out two errors that were inadvertently made in the Patent Term Extension Application: The first error is that the chemical structure for the approved product on page 2 of the Application was inadvertently drawn incorrectly. The second error is that the chemical formula shown on page 4 of the Application as representing the formula in Claim 1 of Patent '031 was inadvertently drawn incorrectly. In a telephone conversation on May 12, 2005, Applicant's undersigned attorney advised Ms. Karin Ferriter of the United States Patent Office of said inadvertent errors, and Ms. Ferriter kindly advised that Applicant file this Supplement.

As explained in the following Remarks, neither inadvertent error substantively affects Applicant's Patent Term Extension Application.

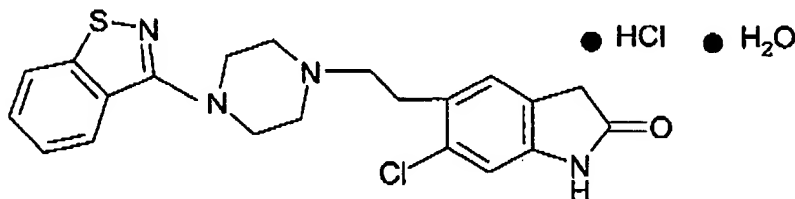
Attorney Docket No. PC7180

Remarks

Page 1 of the Patent Term Extension Application states that the approved product is "GEODON Capsules (ziprasidone hydrochloride monohydrate)". Page 2 of the Patent Term Extension Application shows the "Chemical Formula" for ziprasidone hydrochloride monohydrate as:



The correct chemical formula for ziprasidone hydrochloride monohydrate is:



Note that the linkage between the piperazine moiety and the oxindolyl moiety is an ethylene in the correct chemical formula, as opposed to a methylene in the incorrect formula drawn on page 2 of the Patent Term Extension Application.

Applicant submits that it is apparent that the chemical formula drawn for ziprasidone hydrochloride monohydrate on page 2 of the Patent Term Extension Application is an inadvertent error, and that the correct chemical formula for ziprasidone is as drawn in the immediately preceding paragraph. This is made apparent by the "chemical names" for ziprasidone hydrochloride monohydrate also provided on page 2 of the Patent Term Extension Application, all of which indicate an ethylene, not a methylene, linkage between the piperazine and the 6-chloro-1,3-dihydro-2H-indol-2-one moiety. Specifically, the following three chemical names are provided on page 2 of the Patent Term Extension Application:

5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-

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dihydro-2H-indol-2-one hydrochloride monohydrate.

5-(2-(4-(1,2-benzisothiazol-3-yl)piperazinyl)ethyl)-6-chlorooxindole hydrochloride.

5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one monohydrochloride monohydrate.

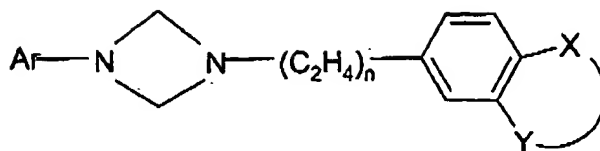
Since the chemical names for ziprasidone in the Patent Term Extension Application do not correspond to the chemical formula for ziprasidone on page 2, it is apparent that an inadvertent error was made.

Further, the correct structure of ziprasidone was known at the time the Patent Term Extension Application was filed with the Patent Office. For example, U.S. Patent 5,935,960 (hereinafter "Patent '960"), which issued August 10, 1999, before the subject Patent Term Extension Application was filed on March 30, 2001, refers to 5-(2-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)ethyl)-6-chloro-1,3-dihydro-2H-indol-2-one as ziprasidone (see Column 1, lines 19-21, of Patent '960"). For convenience, a copy of Patent '960 is attached hereto. Patent '960 also provides a drawing, "Formula II", of the chemical formula of ziprasidone (Formula II, Column 3 and also Column 4). The structure shown on page 2 of the Patent Term Extension Application is not the structure of Formula II, i.e. ziprasidone, from Patent '960. Rather, the structure of Formula II corresponds to the three chemical names given for ziprasidone on page 2 of the Patent Term Extension Application.

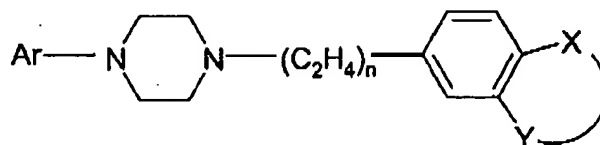
Since it was apparent from the Patent Term Extension Application that either the chemical formula on page 2 or the chemical names in the Patent Term Extension Application were erroneous, and since the structure of ziprasidone was known at the time the Patent Term Extension Application was filed and corresponded to the chemical names in the Patent Term Extension Application, the inadvertent error in the chemical structure of ziprasidone on page 2 of the Patent Term Extension was apparent and was therefore inconsequential.

The second inadvertent error in the subject Patent Term Extension Application is that the chemical structure drawn on page 4 of Patent Term Extension Application as being the chemical structure of Claim 1 of Patent '031 is incorrect. Page 4 of the Patent Term Extension Application indicates that the chemical structure of Claim 1 is:

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The correct chemical structure of Claim 1 of Patent '031 is:



Note that the chemical structure on page 4 of the Patent Term Extension Application erroneously depicts a 4-membered heterocyclic ring with two nitrogens and two carbons, as opposed to the 6-membered piperazine moiety which should have been depicted.

However, a copy of Patent '031 was attached to the Patent Term Extension Application as an Appendix when it was filed with the United States Patent Office. Therefore, the error in the chemical formula of Claim 1 of Patent '031 in the Patent Term Extension Application was apparent and was therefore inconsequential.

If a telephone interview would be of assistance in the prosecution of the subject Patent Term Extension Application, invitation is hereby extended to telephone the undersigned at the number provided.

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No fee is believed necessary in connection with the filing of this Supplement. However, if any fee is determined necessary in connection with the filing of this Supplement, authorization to charge such fee to Deposit Account No. 16-1445 is hereby given.

Respectfully submitted,

Date: July 26, 2005



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US005935960A

**United States Patent** [19]

Walinsky et al.

[11] Patent Number: 5,935,960

[45] Date of Patent: Aug. 10, 1999

[54] PRO-DRUGS OF 5-(2-(4-(1,2-BENZISOTHIAZOL-3-YL)-1-PIPERAZINYL)ETHYL)-6-CHLORO-1,3-DIHYDRO-2H-INDOL-2-ONE.

[75] Inventors: Stanley W. Walinsky, Mystic, Conn.;  
John F. Lambert, Stonington, Conn.

[73] Assignee: Pfizer Inc., New York, N.Y.

[21] Appl. No.: 08/798,395

[22] Filed: Feb. 7, 1997

**Related U.S. Application Data**

[60] Provisional application No. 60/011,568, Feb. 13, 1996.

[51] Int. Cl.<sup>o</sup> ..... A61K 31/495; C07D 403/06

[52] U.S. Cl. .... 514/253; 544/373

[58] Field of Search ..... 544/373, 368;  
514/253

[56] **References Cited****U.S. PATENT DOCUMENTS**

5,312,925 5/1994 Allen et al. .... 544/368  
5,359,068 10/1994 Urban ..... 544/368

**FOREIGN PATENT DOCUMENTS**

790236 8/1997 European Pat. Off. .

*Primary Examiner*—Richard L. Raymond

*Assistant Examiner*—Ann M. Kessinger

*Attorney, Agent, or Firm*—Peter C. Richardson; Paul H. Ginsburg; B. Timothy Creagan

[57] **ABSTRACT**

The present invention relates to a pro-drug of ziprasidone or pharmaceutically acceptable salts thereof, processes for its preparation, and pharmaceutical compositions and methods of treatment comprising said pro-drug.

9 Claims, No Drawings

5,935,960

1

**PRO-DRUGS OF 5-(2-(4-(1,2-BENZISOTHAZOL-3-YL)-1-PIPERAZINYL)ETHYL)-6-CHLORO-1,3-DIHYDRO-2H-INDOL-2-ONE**

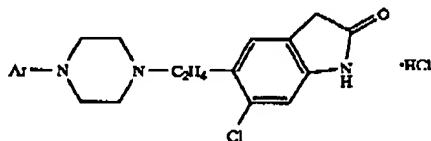
This application claims the priority benefits of United States Provisional Application No. 60/011,568 filed on Feb. 13, 1998.

**BACKGROUND OF THE INVENTION**

The present invention relates to the compound 1-[2-(6-chloro-2,3-dihydro-2-oxo-1H-indol-5-yl)ethyl]-4-[imino(2-mercaptophenyl)methyl]piperazine or one of its pharmaceutically acceptable salts, to processes for its preparation, to pharmaceutical compositions and to methods of treatment. 1-[2-(6-chloro-2,3-dihydro-2-oxo-1H-indol-5-yl)ethyl]-4-[imino(2-mercaptophenyl)methyl]piperazine is a pro-drug of 5-(2-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)ethyl)-6-chloro-1,3-dihydro-2H-indol-2-one (hereinafter referred to as ziprasidone). The compound of the invention, 1-[2-(6-chloro-2,3-dihydro-2-oxo-1H-indol-5-yl)ethyl]-4-[imino(2-mercaptophenyl)methyl]piperazine, has neuroleptic activity and is therefore useful as an antipsychotic.

The aqueous solubility of the dihydrochloride salt of 1-[2-(6-chloro-2,3-dihydro-2-oxo-1H-indol-5-yl)ethyl]-4-[imino(2-mercaptophenyl)methyl]piperazine at about 25° C. is about 25 mg/mL which is approximately 300 times higher than ziprasidone hydrochloride (8.0 µg/mL).

U.S. Pat. No. 4,831,031, issued May 16, 1989, which is hereby incorporated by reference in its entirety, discloses 5-(2-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)ethyl)-6-chloro-1,3-dihydro-2H-indol-2-one hydrochloride, which has the formula



wherein Ar is benzisothiazol-3-yl, in the hemihydrate form (hereafter "the hemihydrate").

U.S. Pat. No. 5,312,925 issued May 17, 1994, which is hereby incorporated by reference in its entirety, refers to the monohydrate hydrochloride salt of ziprasidone, processes for its preparation, and pharmaceutical compositions and methods of treating psychotic disorders.

U.S. Pat. No. 5,359,068, issued Oct. 25, 1994, which is hereby incorporated by reference in its entirety, refers to processes and intermediates for the preparation of ziprasidone.

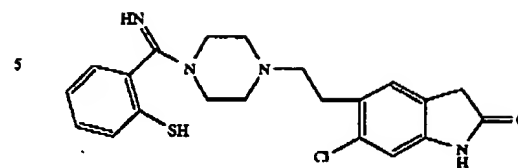
U.S. Pat. No. 5,206,366, issued Apr. 27, 1993, which is hereby incorporated by reference in its entirety, refers to an aqueous based process for preparing ziprasidone.

U.S. Patent Application 60/006,301, filed Nov. 7, 1995, refers to the preparation of 1-(1,2-benzisothiazol-3-yl)piperazine which is a key intermediate in the preparation of ziprasidone.

**SUMMARY OF THE INVENTION**

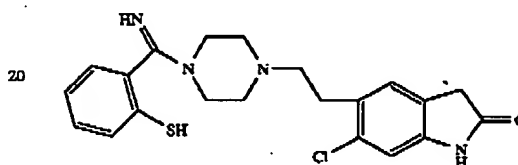
The present invention relates to a compound of the formula

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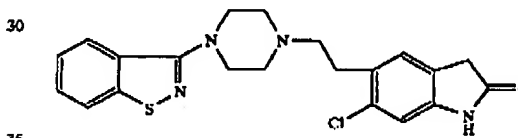


or pharmaceutically acceptable salts thereof.

The present invention also relates to a process for preparing a compound of the formula



comprising reacting a compound of the formula



with a reducing agent. Preferably, the reducing agent is benzyl mercaptan (more preferably 2.2 equivalents of benzyl mercaptan relative to the amount of ziprasidone). In a more preferred embodiment of the invention, a solvent is added to facilitate the reaction. Preferably the solvent is isopropanol. Most preferably, the reaction is run at about 85° C. for about 6 hours.

This invention also relates to a pharmaceutical composition having neuroleptic activity comprising, the compound of formula I in an amount effective in the treatment of neuroleptic diseases, and a pharmaceutically acceptable carrier.

This invention also relates to a method of treating neuroleptic diseases which comprises, administering to a subject in need of treatment a neuroleptic amount of a compound of formula I.

Bisulfite when used herein refers to sodium bisulfite (NaHSO<sub>3</sub>) or potassium bisulfite (KHSO<sub>3</sub>).

Metabisulfite when used herein refers to sodium metabisulfite (Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>) or potassium metabisulfite (K<sub>2</sub>S<sub>2</sub>O<sub>3</sub>).

**DETAILED DESCRIPTION**

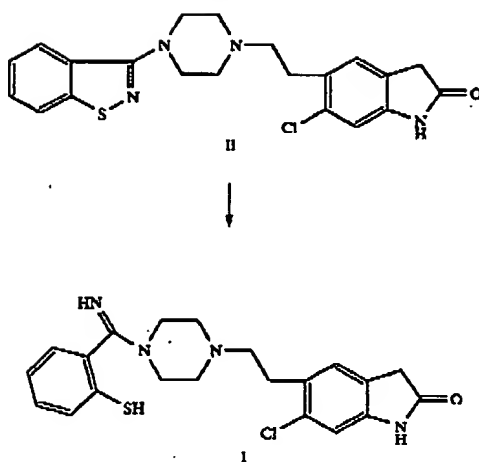
The compounds of the formula I and ziprasidone can be prepared as described in the following reaction Schemes and discussion. Unless otherwise indicated, compounds of the formulae I and II in the reaction Schemes and discussion are as defined above.

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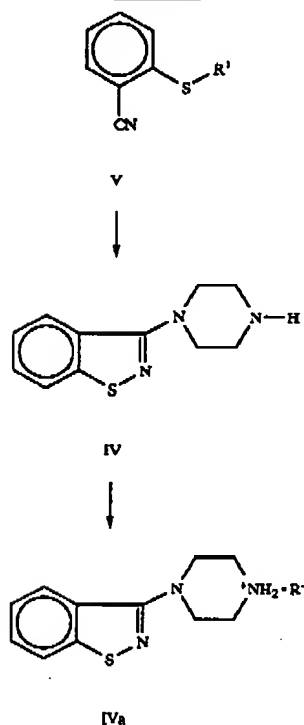
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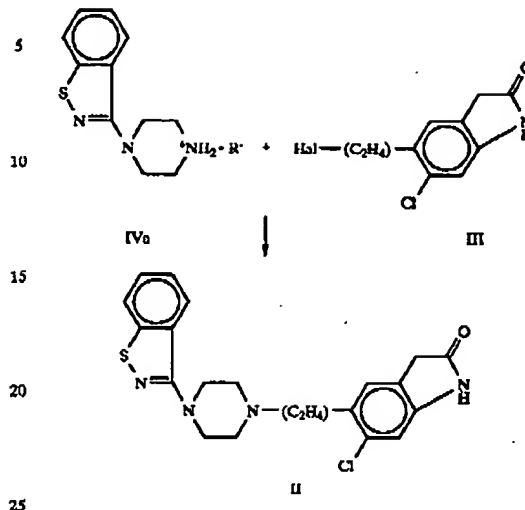
SCHEME 1



SCHEME 2



SCHEME 3

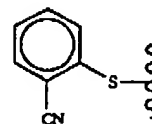


Scheme 1 refers to the preparation of 1-[2-(6-chloro-2,3-dihydro-2-oxo-1H-indol-5-yl)ethyl]-4-[[imino(2-mercaptophenyl)methyl]piperazine from ziprasidone. Ziprasidone can be prepared according to the procedures of Schemes 2 and 3 as well as by other methods described below.

Referring to Scheme 1, ziprasidone is treated with a reducing agent at a temperature from about 50° C. to about 150° C., preferably about 85° C., for about 3 to about 10 hours, preferably about 6 hours. Suitable reducing agents include benzyl mercaptan, lower alkyl mercaptans (such as t-butyl mercaptan, methyl mercaptan, butylmercaptan), bisulfites and metabisulfites. Preferably the reducing agent is benzyl mercaptan. The reducing agent preferably comprises about 1 to about 4 equivalents (relative to the amount of ziprasidone) preferably about 2.2 equivalents. Preferably a solvent is added to facilitate the reaction. Suitable solvents include alcohols (such as isopropanol, t-butanol, methanol or ethanol), or tetrahydrofuran, preferably isopropanol. The solvent is preferably about 5 to about 15 volumes (relative to the weight of ziprasidone). Most preferably, the solvent is about 10 volumes (relative to the weight of ziprasidone).

Scheme 2 refers to the preparation of intermediates of the formula IV which are useful in the synthesis of ziprasidone, as described in U.S. Patent Application, 60/006,301 filed Nov. 7, 1995. These intermediates of the formula IV or IVa which can be converted into ziprasidone, by the methods of Scheme 3.

Referring to Scheme 2, a compound of the formula V, wherein R<sup>1</sup> is



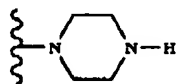


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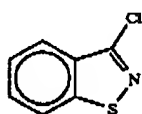
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is commercially available or can be prepared according to the method of Japanese Patent Publication 6,220,030, published Aug. 9, 1994.

A compound of the formula V wherein R<sup>1</sup> is

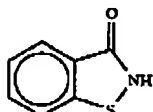


may be prepared by reacting a compound of the formula



with about 1 to about 10 equivalents of piperazine, preferably about 2 to about 5 equivalents of piperazine is used. The temperature of the aforesaid reaction is between about 25° C. to about 105° C., preferably about 65° C. The reaction time varies from about 1 hour to about 20 hours, preferably from about 2 to about 6 hours.

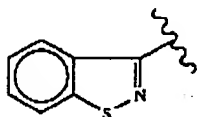
The compound of formula VI is prepared from an amide of the formula



by reaction with about 1 to about 3 equivalents of a chlorinating agent such as phosphorous oxychloride (POCl<sub>3</sub>), phosphorous trichloride (PCl<sub>3</sub>), or phosphorous pentachloride (PCl<sub>5</sub>) in reaction inert solvent. Preferably about 1.2 equivalents of phosphorous oxychloride is used as the chlorinating agent. Suitable solvents include dimethylformamide, dimethylacetamide, or pyridine, preferably dimethylformamide. The reaction time of the aforesaid reaction is from about 1 to about 5 hours, preferably about 3.5 hours. The reaction is performed at a temperature from about 30° C. to about 100° C., preferably about 70° C.

The compound of the formula VII is commercially available.

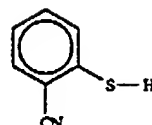
Compounds of the formula V, wherein R<sup>1</sup> is



can be prepared by reacting bis(2-cyanophenyl)disulfide with a compound of the formula

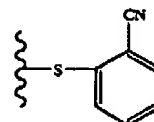
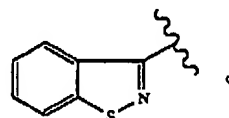
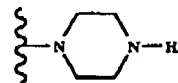
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VIII

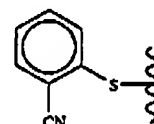


in a reaction inert solvent. Suitable reaction inert solvents include isopropanol, ethanol, or tetrahydrofuran, preferably isopropanol. The temperature of the aforesaid reaction is about 50° C. to about 120° C. The reaction time of the aforesaid reaction is about 1 hour to about 3 hours, preferably about 2 hours.

A compound of the formula V, wherein R<sup>1</sup> is



can be converted into a compound of the formula IV by reaction with from about 2 to about 20 equivalents of piperazine (preferably anhydrous). The preferred amount of piperazine is the amount of piperazine that minimizes bis substitution of the free amine of the piperazine group of the compound of the formula IV. The preferred R<sup>1</sup> is



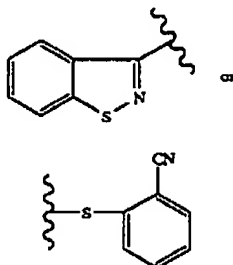
When R<sup>1</sup> is a group of the formula "c", as depicted above, the preferred amount of piperazine is about 5 to 10 equivalents, most preferably about 10 equivalents. The temperature of the aforesaid reaction is between about 76° C. and 200° C., preferably about 120° C. The reaction time varies depending on the temperature at which the reaction is run. As the reaction temperature is increased the reaction time is decreased. When the reaction is run at about 80° C., only small amounts of product are formed after 2 days. When the reaction is run at about 200° C., the vessel must be pressurized to prevent loss of the piperazine and the clearing agent and the ensuing reaction time is about 1 hour. When the reaction is performed at high temperatures, the internal reaction vessel pressure is between about 50 to 60 psi and as such is well within the standard pressure capacities for commercial reactors. When the reaction is performed

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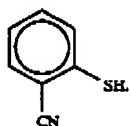
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at the ideal temperature of about 120° C. the reaction time is about 24 hours.

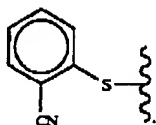
The reaction between a compound of the formula V, wherein R<sup>1</sup> is



and piperazine generates a thiol by-product of the formula



A preferred embodiment of the reaction involves the in situ oxidation of the compound of formula VIII into a compound of the formula V, wherein R<sup>1</sup> is



This in situ oxidation is facilitated by adding from about 1 to about 10 equivalents, preferably 4 equivalents, of an oxidant to the reaction vessel. Suitable oxidants include dimethyl sulfoxide, air, copper (II) salts, bisulfite, metabisulfite or hydrogen peroxide, preferably dimethyl sulfoxide. When dimethyl sulfoxide is the oxidant, preferably about 2 to 5 equivalents are used in the reaction.

In another preferred embodiment of the reaction about 0.5 to about 5 volumes of a piperazine clearing agent is added to the reaction vessel so as to prevent piperazine from solidifying in the head space and vapor lines of the reaction vessel. Suitable piperazine clearing agents have boiling points in the range of about 70° C. to about 130° C., such as isopropanol or t-butanol, pyridine, toluene or diglyme, preferably isopropanol. Preferably about 1.2 volumes (a relative proportion (mL/gm) to the weight of the compound of formula II) of the piperazine clearing agent is used.

A compound of the formula IV can be converted to the more stable pharmaceutically acceptable salts of the formula IVa, wherein R is a pharmaceutically acceptable anion conjugate of a pharmaceutically acceptable acid, by treatment of the free base of formula IV with a pharmaceutically acceptable acid of the formula RH in a polar solvent. Suitable acids of the formula RH are those which form non-toxic acid addition salts, e.g., salts containing pharmacologically acceptable anions, such as chloride, bromide,

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iodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. Preferably the acid is hydrochloric acid. Suitable solvents include lower alcohols, such as methanol, ethanol, isopropanol or t-butanol, toluene, ethers such as diethyl ether or tetrahydrofuran, or mixtures of the above solvents. Preferably the solvent is a mixture of isopropanol and toluene.

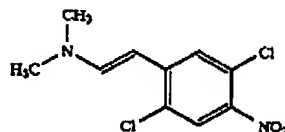
The conversion of the compound of formulae IV or IVa to ziprasidone follows the processes described in U.S. Pat. Nos. 4,831,031, 5,206,366 or 5,359,068, which issued on May 16, 1989, Apr. 27, 1993 and Oct. 25, 1994 respectively.

Scheme 2 refers to the preparation of ziprasidone from compounds of the formula IV or IVa according to the processes described in U.S. Pat. No. 4,831,031, issued May 16, 1989. Specifically, a compound of the formula IV or IVa is reacted with a compound of the formula III wherein Hal is fluoro, chloro, bromo or iodo. This coupling reaction is generally conducted in a polar solvent such as a lower alcohol, for instance ethanol, dimethylformamide or methyl isobutyl ketone, and in the presence of a weak base such as a tertiary amine base, for instance triethylamine or diisopropylethylamine. Preferably, the reaction is performed in the further presence of a catalytic amount of sodium iodide, and a neutralizing agent for hydrochloride such as sodium carbonate. The reaction is preferably conducted at the reflux temperature of the solvent used.

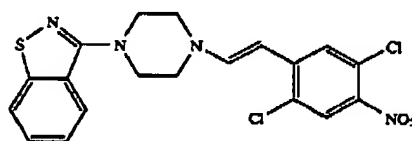
Alternatively, Scheme 2 also refers to the conversion of compounds of formula IV or IVa into ziprasidone by the methods of U.S. Pat. No. 5,206,366, issued Apr. 27, 1993. Specifically, a compound of formula IV or IVa is reacted with a compound of formula III, wherein Hal is fluoro, chloro, bromo or iodo. This coupling reaction is conducted in refluxing water with a hydrohalic acid neutralizer.

Alternatively, compounds of the formula IV can be converted to ziprasidone by the methods described in U.S. Pat. No. 5,359,068, issued Oct. 25, 1994.

Specifically, compounds of the formula I may be reacted with a compound of the formula



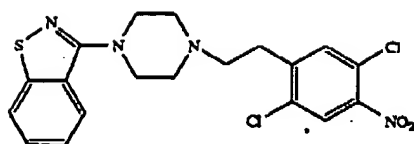
in the presence of a (C<sub>1</sub>-C<sub>6</sub>) alkanolic acid to form the compound of the formula



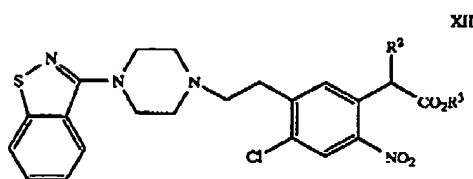
The compound of the formula X can then be treated with a reducing agent to form the compound of the formula

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The compound of the formula XI can then be treated with a compound of the formula  $R^2-CH_2-CO_2R^3$  wherein  $R^2$  is  $CO_2R^3$  or CN and  $R^3$  is  $(C_1-C_6)$ alkyl to form a compound of formula



wherein  $R^2$  is CN or  $CO_2R^3$  and  $R^3$  is  $(C_1-C_6)$ alkyl.

The compound of formula XII can then be treated with an acid at an elevated temperature to form the compound of formula XII wherein  $R^2$  and  $R^3$  are both hydrogen.

The compound of formula XII can then be treated with a  $(C_1-C_6)$ alkanol in the presence of an acidic esterification catalyst to form the compound of formula XII wherein  $R^2$  is hydrogen and  $R^3$  is  $(C_1-C_6)$ alkyl.

The compound of the formula XII, wherein  $R^2$  is hydrogen, CN or  $CO_2R^3$  and  $R^3$  is hydrogen or  $(C_1-C_6)$ alkyl, can then be treated with a reducing agent with the proviso that when  $R^2$  is CN or  $CO_2R^3$  and  $R^3$  is  $(C_1-C_6)$ alkyl the product of the reduction is heated with an acid to form ziprasidone.

Specific details of the reaction steps of converting compounds of the formula IV into ziprasidone can be found in U.S. Pat. No. 5,359,068, issued Oct. 25, 1994.

The compound of formula I possesses potent neuroleptic activity. The compound of formula I is therefore useful in the treatment or prevention of psychotic disorders, such as schizophrenia. The neuroleptic activity of the compound of the invention may be demonstrated by methods well known to those of ordinary skill in the art, such as the methods described in T.F. Seeger, et al., *Journal of Pharmacology and Experimental Therapeutics*, 275, (1), 101-113 (1995). Specifically, the standard methods for determining neuroleptic activity are based on Dopamine D-2, Dopamine D-3, Dopamine D-4, 5-hydroxytryptamine-1A (5-HT-1A), 5-hydroxytryptamine-2C (5-HT-2C), and 5-hydroxytryptamine-2A (5-HT-2A) receptor binding studies. Tissues or membranes used to perform these studies are derived from rat, pig, or from cell lines expressing human receptor subtypes. LTK-cells expressing the human  $D_{2, long}$  receptor were obtained from Dr. Olivier Civelli, Oregon Health Sciences University, Portland, Oreg. Chinese hamster ovary cells (CHO) expressing the human D3 receptor were obtained from Dr. J. C. Schwartz, Unite de Neurobiologie, Institut National de la Sante' et de la Recherche Medicale, 2 ter Rue D'Ale' Sia, Paris, France, 75014.

The following protocol describes one possible method for determining activity for the compound of formula I. Specific assay conditions for each receptor is described in Table 1, below. Tissues or cell lines of interest are homogenized in various buffer solutions (details are given in Table 1) using

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a Brinkman Polytron at setting 6 for 20 sec. Membranes are recovered after multiple rounds of separation by centrifugation and resuspension in fresh ice-cold buffer. The resulting tissue homogenates are added to test tubes containing incubation buffer, various concentrations of test drug, and the appropriate tritiated or iodinated ligand. Non-specific binding is determined by radioligand binding in the presence of a saturating excess of a known competitor for the receptor of interest (as listed in Table 1). After allowing sufficient time to attain equilibrium at the appropriate temperature, incubations are terminated by rapid filtration through Whatman GF/B filters using a Brandel cell harvester. The membranes are washed three times with four ml aliquots of ice-cold buffer. Membrane-bound ligand is determined by liquid scintillation counting of the filters in Ready-Safe scintillation cocktail (for tritiated ligands), or by direct counting in a gamma counter (for  $^{125}I$  ligands). For all receptor types, the dissociation constant ( $K_d$ ) for the radioligand is previously determined by saturation analysis in the tissue of interest, and used to calculate apparent  $K_i$ 's by means of the Cheng-Prusoff equation (Cheng and Prusoff, 1973). In some cases the  $IC_{50}$  concentration (concentration of compound required to displace specific binding by 50%) can be interpolated by linear regression analysis of the concentration-response curves from competition binding studies.

The compound of the invention possessed the receptor binding results depicted in Table 2

TABLE 1

## Assay Conditions for Radioligand Binding Studies

Receptor	Ligand concentration	Tissue	Blank	Buffer pH
Dopamine D-2	3H-spiroperidol 2 nM + 1 μM prazosin + 500 nM cinnaserin	rat caudate	(+)-butaclamol 5 μM	50 mM TrisHCl, 100 mM NaCl 1 mM MgCl <sub>2</sub> pH 7.2
Dopamine D-3	3H-spiroperidol 0.1 nM	human D3-transfected CHO cells	(+)-butaclamol 2 μM	50 mM TrisHCl pH 7.4, 120 mM NaCl, 5 mM KCl, 2 mM MgCl <sub>2</sub> , 2 mM CaCl <sub>2</sub>
Dopamine D-4	3H-spiroperidol 0.1 nM	human D4-transfected COS-7 cells	(+)-butaclamol 2 μM	50 mM TrisHCl pH 7.4, 120 mM NaCl, 5 mM KCl, 2 mM MgCl <sub>2</sub> , 2 mM CaCl <sub>2</sub>
5HT-1A	3H-8OH-DPAT 1.5 nM	rat cortex	serotonin 10 μM	50 mM TrisHCl, 0.1% ascorbate, 4 mM CaCl <sub>2</sub> 10 μM pargyline pH 7.7
5HT-2C <sup>10</sup>	3H-mesulergine 1 nM	pig choroid plexus	serotonin 10 μM	50 mM TrisHCl, 0.1% ascorbate 4 mM CaCl <sub>2</sub> pH 7.7
5HT-2A	3H-	rat frontal	methysergide	50 mM

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TABLE 1-continued

Assay Conditions for Radioligand Binding Studies				
Receptor	Ligand concentration	Tissue	Blank	Buffer pH
	ketanserin 4 nM + 1 $\mu$ M prazosin + 500 nM mepyramine	cortex	2 $\mu$ M	TrisHCl pH 7.7

TABLE 2

Receptor	Radioligand Binding Results
D2	2.3 nM
D3	5.8 nM
D4	59.2 nM
5HT <sub>2</sub>	0.35 nM (IC <sub>50</sub> )
5HT <sub>1A</sub>	12 nM(IC <sub>50</sub> )

Pro-drugs of ziprasidone may be administered as a neuroleptic agent. Administration to a human subject may be alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents in a pharmaceutical composition, in accordance with standard pharmaceutical practice. The pro-drugs of ziprasidone may be administered orally or parenterally including intravenously or intramuscularly. Suitable pharmaceutical carriers include solid diluents or fillers, and sterile aqueous solutions and various organic solvents. The pharmaceutical compositions are then readily administered in a variety of dosage forms, such as tablets, powders, lozenges, syrups, and injectable solutions. These pharmaceutical compositions, if desired, may contain additional ingredients such as flavorings, binders and excipients. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, alginate acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, a solution or suspension of a pro-drug of ziprasidone in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

The effective dosage for a pro-drug of ziprasidone depends on the intended route of administration and other factors such as age and weight of the subject, as generally known.

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The following Examples illustrate the preparation of the pro-drugs of the present invention. Commercial reagents were utilized without further purification. Melting points are uncorrected. NMR data are reported in parts per million ( $\delta$ ) and are referenced to the deuterium lock signal from the sample solvent. Unless otherwise stated, all mass spectrum were performed using electron impact (EI, 70 eV) conditions. Unless otherwise indicated, chromatography refers to column chromatography performed using 32–63,  $\mu$ m silica gel and executed under nitrogen pressure (flash chromatography) conditions. High Pressure Liquid Chromatography (HPLC) was performed on a LDC Analytical constaMetric® 3200 HPLC (Thermo Separation Products Co.). A Zorbax®C8, 60Å, 3.9×150 mm column (Mac-Mod Analytical, Inc., Chadds Ford, Pa. 19317) was used for HPLC analysis (mobile phase: 40% acetonitrile, 45% 0.05M potassium phosphate, monobasic (KH<sub>2</sub>PO<sub>4</sub>) adjusted to pH=6.0 with potassium hydroxide (KOH), 15% methanol; Flow Rate of 1.0 ml/minute; Detector: UV 229 nm; Injector: 10  $\mu$ l; Samples are prepared in mobile phase (0.05 mg/ml)). Room temperature refers to 20–25° C.

## EXAMPLE 1

## 1-[2-(6-Chloro-2,3-dihydro-2-oxo-1H-indol-5-yl)ethyl]-4-[(imino(2-mercaptophenyl)methyl)piperazine

A one-liter, 3-neck round bottom flask equipped with a mechanical stirrer, condenser topped with a nitrogen inlet, and thermometer was purged and then maintained under an inert nitrogen atmosphere. 5-[2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one (60.0 g, 145 mmol), 2-propanol (600 mL), and benzyl mercaptan (45.1 g, 363 mmol) were added to the flask affording a pink slurry which was heated to reflux (83° C.). After 6 hours at reflux, thin layer chromatography (eluted with methylene chloride/isopropanol 4:1) showed that the reaction was complete. The slurry was cooled to 25° C. and then granulated overnight. The slurry was filtered and the filter cake was washed with isopropanol (two times 90 mL). The wet cake was suspended in one liter of tetrahydrofuran (THF) and the resulting slurry was granulated at 25° C. for 7 hours. The slurry was filtered, washed with THF (two times 100 mL), and then dried in vacuo at 42° C. overnight. The title compound (54.4 g) was isolated as a tan solid (mp=224–226° C. with decomposition) in 90.2% yield. <sup>13</sup>C NMR (DMSO-d<sub>6</sub>):  $\delta$  176.25, 166.33, 159.16, 143.28, 135.16, 131.84, 131.26, 129.64, 128.65, 126.88, 126.03, 125.21, 116.37, 109.58, 57.65, 51.58, 35.40, and 29.95. Dibenzyl disulfide was isolated as a reaction by-product from the mother liquors.

## EXAMPLE 2

## 1-[2-(6-Chloro-2,3-dihydro-2-oxo-1H-indol-5-yl)ethyl]-4-[(imino(2-mercaptophenyl)methyl)piperazine dihydrochloride

The compound (5.0 g, 12.1 mmol) from Example 1 was suspended in 75 mL of THF at room temperature, and then 1.97 mL of concentrated hydrochloric acid was slowly added over 30 min affording a gummy solid. Water (5 mL) was added and the gummy solids were stirred for 6 hours to produce a finely divided solid which was granulated overnight. The mixture was filtered and the filter cake was washed with THF (10 mL). The product was dried in vacuo at 25° C. overnight under a nitrogen bleed to give 5.87 g of the title dihydrochloride compound as a tan solid (mp=232–240° C. with decomposition). When the dihydrochloride

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ride was titrated with 0.2032 Molar sodium hydroxide, it showed pH equivalents points at 4.33 and 8.22 ( $pK_a=3.1$  and 5.5).

#### PREPARATION 1

##### 3-(1-Piperazinyl)-1,2-benzisothiazole hydrochloride Method A

Bis(2-cyanophenyl)disulfide (20.0 g, 74.5 mmol), anhydrous piperazine (64.2 g, 745 mmol), dimethyl sulfoxide (12.8 g, 164 mmol), and isopropanol (24 mL) were added to a 500 mL round bottom flask equipped with a mechanical stirrer, thermometer, condenser topped with a nitrogen inlet and a connector leading to a bleach scrubber. After the flask was purged with nitrogen, the reactants were melted (at approximately 80° C.) and then heated to reflux (110–126° C.). After 24 hours at reflux, the reddish solution was sampled for thin-layer chromatography (elution with methylene chloride/isopropanol/triethylamine, 15:5:1) which showed that the reaction was complete. The solution was cooled to 85–90° C., at which point water (130 mL) was added. The resulting slurry was cooled to 30–35° C. The reaction mixture was then concentrated at reduced pressure (bp=50–60° C. at 110 mm) to remove approximately 30 mL of distillate. The distillate was treated with bleach to destroy the dimethyl sulfide (DMS). Dräger tubes (Drägerwerk AG Lübeck, Germany), which are selective for detecting ppm levels of dimethyl sulfide, showed that the reaction's headspace vapors contained less than 1 ppm residual DMS. A sample of the crude reaction mixture was analyzed by HPLC. The crude reaction mixture contained 3-(1-piperazinyl)-1,2-benzisothiazole (80%), 3,3'-(1,4-piperazinyl)-bis-1,2-benzisothiazole (4.6%), and 2-(1-piperazinyl)pyrazine (4%). After isopropanol (28 mL) and water (71 mL) were added, the slurry was cooled to 30° C., granulated for 0.5 hour, and then filtered through diatomaceous earth, e.g., Celite®, to remove 3,3'-(1,4-piperazinyl)-bis-1,2-benzisothiazole. The filter cake was washed with 56 mL of an isopropanol/water (1:1) solution. Toluene (170 mL) was added to the warm (32° C.) filtrate, and then the separated aqueous layer was washed with fresh toluene (100 mL). The combined toluene layers were washed with water (100 mL) and then treated with decolorizing carbon, e.g., DARCO KB-B®, (2 g). The Celite® cake was rinsed with toluene (60 mL), and the combined wash and filtrate were concentrated at reduced pressure to 90 mL. Isopropanol (220 mL) was added to the concentrate and the yellowish solution was cooled to 20° C. The pH of the solution was slowly adjusted to 3.5–4.0 with 9.8 mL of concentrated hydrochloric acid. The resulting slurry was cooled to 0–5° C., granulated for 1 hour, and then filtered. The product cake was washed with cold isopropanol (80 mL), and then dried in vacuo at 40° C. for 24 hours. The title compound (43.2 g) was isolated as a light yellow solid in 77.6% yield (98.5% hplc purity). The spectroscopic and physical properties of the solid were identical to an authentic sample (Caution: compound is a strong irritant). <sup>1</sup>H NMR (D<sub>2</sub>O): δ 7.80 (m, 2H), 7.49 (m, 1H), 7.35 (m, 1H), 3.58 (m, 4H), and 3.42 (m, 4H).

<sup>13</sup>C NMR (dimethyl sulfoxide): δ 162.72, 152.10, 128.15, 127.09, 124.63, 124.12, 121.21, 48.48, and 42.49.

#### PREPARATION 2

3-(1-Piperazinyl)-1,2-benzisothiazole • hydrochloride  
Bis(2-cyanophenyl)disulfide (5.00 g, 18.6 mmol), anhydrous piperazine (8.02g, 93.2 mmol), and isopropanol (5

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mL) were combined under nitrogen and heated to reflux (115° C.). The yellow solution was heated at reflux (110–115° C.) for 23 hours and then cooled to 95° C. Water (30 mL) was added and the resulting suspension was cooled to 25° C. and filtered. The filter cake was washed with 12 mL of water/isopropanol solution (2:1). Toluene (50 mL) was then added to the combined wash and filtrate. The toluene layer was separated and the aqueous layer extracted with additional toluene (25 mL). The combined toluene layers were washed with water (20 mL), treated with activated charcoal (DARCO KB-B®) (0.5 g), filtered, and then concentrated at reduced pressure (42° C. at 700 mm Hg) to 12 mL. Isopropanol (30 mL) was added to the concentrate and then the pH was adjusted to 4.4 with concentrated hydrochloric acid. The resulting slurry was cooled to 0–5° C., granulated for 1 hour, and then filtered. The product cake was washed with cold isopropanol (10 mL) and dried in vacuo at 42° C. to give 3.22g (34% overall yield) of 3-(1-piperazinyl)-1,2-benzisothiazole. The product was a single spot by thin-layer chromatography.

The pH of the aqueous layer was adjusted to 4.0 with concentrated hydrochloric acid, and then extracted with methylene chloride (40 mL). The methylene chloride solution was concentrated at reduced pressure to an oil which was then dissolved in methanol (19 mL). The solution was cooled in an ice bath and 10% aqueous hydrogen peroxide solution (7 mL) was added with stirring. After stirring for 10 minutes, thin-layer chromatography showed that the reaction was complete. Water (12 mL) was added and the slurry was granulated for 1.5 hours. Product was filtered and dried in vacuo at 40° C. to recover 1.64 grams (33% recovery) of bis(2-cyanophenyl)disulfide for recycle.

#### PREPARATION 3

##### 3-(1-Piperazinyl)-1,2-benzisothiazole • hydrochloride

Anhydrous piperazine (49.4 g, 0.57 mol) and t-butanol (10 mL) were added to a dry, 300 mL round bottom flask equipped with a mechanical stirrer, thermometer, condenser topped with a nitrogen inlet, and pressure-equalizing dropping funnel. After the flask was purged with nitrogen, it was heated to 100° C. in an oil bath. A solution of 3-chloro-1,2-benzisothiazole (19.45 g, 0.11 mol) in t-butanol (10 mL) was added to the addition funnel, and then slowly added to the reaction flask over 20 minutes to moderate an exothermic reaction (112–118° C.). Once addition was complete the yellow solution was heated to reflux (121° C.) and then maintained at reflux for 24 hours. Thin-layer chromatography showed that the reaction was complete. The reaction mixture was cooled to 85° C. and 120 mL of water was added. The hazy solution was filtered and the filter cake rinsed with 60 mL of t-butanol/water (1:1) solution. The pH of the combined filtrate and wash was adjusted to 12.2 with 50% aqueous caustic. The aqueous solution was extracted with toluene (200 mL), the layers were separated, and the aqueous layer was extracted with fresh toluene (100 mL). The combined toluene layers were washed with water (75 mL), and then the toluene solution was concentrated in vacuo at 48° C. to 90 mL. Isopropanol (210 mL) was added to the concentrate and then the pH was slowly adjusted to 3.8 with 7.6 mL of concentrated hydrochloric acid. The resulting slurry was cooled to 0° C., granulated for 45 min, and then filtered. The filter cake was washed with cold isopropanol (50 mL) and then dried in vacuo at 40° C. to afford 23.59 g (80% yield) of 3-(1-piperazinyl)-1,2-benzisothiazole hydrochloride as an off white solid.

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## PREPARATION 4

## 3-(1-Piperazinyl)-1,2-benzisothiazole

3-(2-Cyanophenylthio)-1,2-benzisothiazole (0.25 g, 0.93 mmol), anhydrous piperazine (0.80, 9.32 mmol), and isopropanol (0.25 mL) were added to a 6 mL round bottom flask equipped with a magnetic stirring bar, reflux condenser topped with a nitrogen inlet, and thermometer. The flask was purged with nitrogen and then immersed in a 120° C. oil bath to give a yellow refluxing solution. After heating at 116–120° C. 120° C. for 25 hours, the reddish solution was cooled to 25° C. and 5 mL of methanol was added. Thin-layer chromatography (methylene chloride/isopropanol/triethylamine, 15:5:1) showed that the reaction was essentially complete. The crude reaction solution was analyzed by high-pressure liquid chromatography to show that 3-(1-piperazinyl)-1,2-benzisothiazole was formed in 70% yield.

## PREPARATION 5

## 3-(1-Piperazinyl)-1,2-benzisothiazole

Anhydrous piperazine (17.2 g, 0.20 mol) and isopropanol (3.0 mL) were charged to a round bottom flask equipped with a mechanical stirrer, thermometer, condenser topped with a nitrogen inlet, and an addition funnel. Once the flask was purged and then maintained under nitrogen, the mixture was heated to 90° C. to afford a solution. A solution of 1-(2-cyanophenylthio)piperazine (4.38 g, 20.0 mmol) in isopropanol (2.0 mL) was slowly added to the warm piperazine solution over 1 hour. Once the addition was complete, the solution was heated to reflux (118° C.) for 24 hours. The reddish solution was cooled to room temperature and then analyzed by HPLC. 3-(1-Piperazinyl)-1,2-benzisothiazole was formed in 55% yield by HPLC assay.

## PREPARATION 6

## 3-(2-Cyanophenylthio)-1,2-benzisothiazole

## Method A

Bis(2-cyanophenyl)disulfide (1.25 g, 4.66 mmol), anhydrous piperazine (4.01 g, 46.6 mmol), and dimethyl sulfoxide (0.80 g, 10.3 mmol) in 15 mL of tetrahydrofuran were added to a 50 mL round bottom flask equipped with a magnetic stirring bar, thermometer, and condenser topped with a nitrogen inlet. After the flask was purged with nitrogen, the mixture was heated at reflux (75° C.) for 25 hours. The reaction mixture was cooled to 25° C., and the tetrahydrofuran was removed at reduced pressure. The resulting solid was dissolved in a 40 mL of a methylene chloride/water (1:1) mixture, the layers were separated, and the organic layer washed with water (20 mL). The methylene chloride solution was evaporated to afford a crude solid (0.85 g) which was crystallized from isopropanol (17 mL) to give light yellow crystals. After filtration, the product was dried in vacuo at 40° C. to give 0.39 g (31% yield) of 3-(2-cyanophenylthio)-1,2-benzisothiazole. Melting point 115.5–117° C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.03 (m, 1H), 7.92 (m, 1H), 7.77 (m, 1H), 7.70 (m, 1H), 7.57 (m, 2H), and 7.48 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 154.99, 152.30, 134.83, 134.56, 134.06, 133.24, 129.07, 128.51, 125.33, 123.29, 120.13, 117.13, and 116.95. Analytical calculated for C<sub>14</sub>H<sub>8</sub>N<sub>2</sub>S<sub>2</sub>: C, 62.66; H, 3.00; N, 10.44; S, 23.90. Found: C, 62.43; H, 3.01; N, 10.68; S, 24.05. A X-ray crystal structure was also obtained to confirm structure.

## PREPARATION 7

## 3-(2-Cyanophenylthio)-1,2-benzisothiazole

## Method B

Bis(2-cyanophenyl)disulfide (0.40 g, 1.48 mmol) and 2-mercaptobenzonitrile (0.20 g, 1.48 mmol) were combined

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in 2 mL of isopropanol and were heated at reflux (90° C.) for 25 hours under a nitrogen (N<sub>2</sub>) atmosphere. 3-(2-Cyanophenylthio)-1,2-benzisothiazole was formed in 69% yield by HPLC assay.

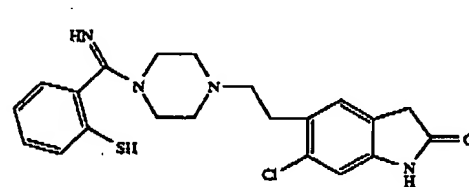
## PREPARATION 8

## 1-(2-Cyanophenylthio)piperazine

Anhydrous piperazine (22.5 g, 261 mmol) and tetrahydrofuran (100 mL) were combined under a nitrogen atmosphere and then heated to 60–65° C. 3-Chloro-1,2-benzisothiazole (10.0 g, 59.0 mmol) was slowly added over one hour to the warm piperazine solution and then the resulting reddish solution was heated at 65° C. for 17 hours. Thin-layer chromatography (ethyl acetate/hexanes/triethylamine, 10:10:1) showed that the reaction was complete. The mixture was cooled to room temperature and then filtered. After toluene (100 mL) was added, the solution was concentrated at reduced pressure (40° C.) to one-half volume. The toluene solution was washed with water (100 mL), and the aqueous layer was extracted with fresh toluene (25 mL). The combined toluene layers were concentrated at reduced pressure to about 30 mL. After cooling the solution to 0–5° C., hexanes (50 mL) was slowly added. The resulting crystals were granulated for 1 hour at 0 to 5° C., filtered, and the cake was washed with fresh hexanes (15 mL). After drying the solids for 18 hours at 23° C., 11.51 grams (89% yield) of a yellow crystalline solid (m.p.=67–71° C.) was isolated. The crude sulfenamide contained approximately 5% of 1,4-bis(2-cyanophenylthio)piperazine by NMR analysis. Title sulfenamide was stored at 0 to –10° C. to prevent slow conversion to 1,4-bis(2-cyanophenylthio)piperazine with heating or storage at room temperature. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.63 (m, 1H), 7.56 (m, 3H), 7.21 (m, 1H), 2.96 (m, 4H), and 2.87 (m, 4H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 142.69, 133.55, 132.67, 128.14, 126.69, 116.80, 110.24, 57.34, and 47.06. HRMS Found: 220.0878; C<sub>11</sub>H<sub>13</sub>N<sub>3</sub>S Requires (FAB P+1): 220.0908.

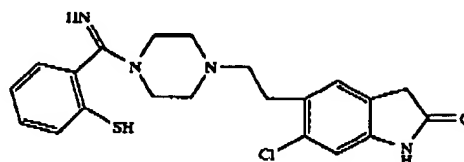
We claim:

1. A compound of the formula



or a pharmaceutically acceptable salt thereof.

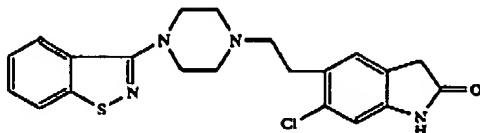
2. A process for preparing a compound of the formula



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comprising, reacting a compound of the formula



with a reducing agent.

3. A process according to claim 2 wherein said reducing agent is benzyl mercaptan.

4. A process according to claim 3 wherein said reducing agent benzyl mercaptan comprises 2.2 equivalents relative to the amount of ziprasidone.

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5. A process for according to claim 4 wherein said reaction is performed in the presence of a solvent.

6. A process according to claim 5 wherein said solvent is isopropanol.

7. A process according to claim 6 wherein said reaction is run at about 85° C. for about 6 hours.

8. A pharmaceutical composition having neuroleptic activity comprising the compound according to claim 1 in an amount effective in the treatment of neuroleptic diseases, and a pharmaceutically acceptable carrier.

9. A method of treating neuroleptic diseases which comprises administering to a subject in need of such treatment a neuroleptic amount of the compound according to claim 1.

\* \* \* \* \*

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Date: July 26, 2005

Time (New York)

Docket No. PC7180

By KLK:mr

Patent No. 4,831,031

Issued May 16, 1989

To John A. Lowe III, et al.

Entitled ARYL PIPERAZINYL (C2 OR C4) ALKYLENE HETEROCYCLIC COMPOUNDS HAVING NEUROLEPTIC ACTIVITY

Application Serial No. 06/146,886

Filed January 22, 1988

The following has been received by the Patent Office in connection with the above - identified patent application on the date of this facsimile transmission, which is indicated above:

☒ Supplement to March 30, 2001 Patent Term Extension Application.

☒ Copy of U.S. Patent 5,935,960.

☒ Certificate of Facsimile Transmission dated 07/26/05.